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Course of Cognitive Development From Infancy to Early Adulthood in the Psychosis Spectrum

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Supplemental content

IMPORTANCE Most patients with psychotic disorders experience severe cognitive impairment, but the onset and course of this impairment remain unclear. Moreover, the course of cognitive functions in other psychiatric conditions remains largely unexamined.

OBJECTIVE To chart the course of general and specific cognitive functions in individuals with psychotic disorders, psychotic experiences, and depression.

DESIGN, SETTING, AND PARTICIPANTS The Avon Longitudinal Study of Parents and Children (ALSPAC) is a prospective cohort study comprising all live births between April 1, 1991, and December 31, 1992, in Avon, England. The dates of analysis were September 2015 to July 2016. Participants who underwent cognitive testing at ages 18 months and 4, 8, 15, and 20 years and psychiatric assessment at age 18 years were included.

MAIN OUTCOMES AND MEASURES Individuals with psychotic disorder, psychosis with depression, psychotic experiences, and depression were compared with controls. Outcomes were full-scale, verbal, and nonverbal IQ at ages 18 months and 4, 8, 15, and 20 years, as well as measures of processing speed, working memory, language, visuospatial ability, and attention at ages 8 and 20 years.

RESULTS The following numbers of individuals were available for analyses in this longitudinal birth cohort study: 511 (238 male [46.6%]) at age 18 months (mean [SD] age, 1.53 [0.03] years), 483 (229 male [47.4%]) at age 4 years (mean [SD] age, 4.07 [0.03] years), 3930 (1679 male [42.7%]) at age 8 years (mean [SD] age, 8.65 [0.29] years), 3783 (1686 male [44.6%]) at age 15 years (mean [SD] age, 15.45 [0.27] years), and 257 (90 male [35.0%]) at age 20 years (mean [SD] age, 20.06 [0.55] years). Individuals with psychotic disorder showed continually increasing deficits between infancy (18 months) and adulthood (20 years) in full-scale IQ (effect size of change [ESΔ] = −1.09, P = .02) and nonverbal IQ (ESΔ = −0.94, P = .008). The depression group showed a small, increasing deficit in nonverbal IQ (ESΔ = −0.29, P = .04) between infancy and adulthood. Between ages 8 and 20 years, the psychotic disorder group exhibited developmental lags (ie, slower growth) in measures of processing speed (ESΔ = −0.68, P = .001), working memory (ESΔ = −0.59, P = .004), and attention (ESΔ = −0.44, P = .001) and large, static deficits in measures of language (ES = −0.87, P = .005) and visuospatial ability (ES = −0.90, P = .001). There was only weak evidence for cognitive deficits in the psychosis with depression group and the psychotic experiences group.

CONCLUSIONS AND RELEVANCE The findings herein suggest that the origins of psychotic disorder involve dynamic developmental processes, affecting both verbal and nonverbal abilities throughout the first 2 decades of life and leading to increasing dysfunction. These developmental processes do not manifest in other psychiatric disorders, such as psychosis with depression and depression.

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Cognitive impairment is a core feature of schizophrenia.[1,2] Understanding its nature and course will help elucidate the pathophysiological processes that lead to the disorder.

There is clear evidence for cognitive deficits in children and adolescents who later have schizophrenia, with an estimated mean premorbid deficit of 8 IQ points.[3] A larger mean deficit of approximately 14 IQ points has been reported in adults with schizophrenia even at the first episode.[4] Longitudinal studies investigating IQ change from before to after illness onset have shown evidence of increasing cognitive impairment[5] as well as distinct premorbid trajectories between cognitive functions.[6] Therefore, the extent and course of premorbid impairment may differ between functions. While verbal deficits have shown a static course, emerging early and remaining stable, processing speed and working memory abilities have shown slower growth over time, resulting in increasing lags.[6]

Important questions remain regarding the course of cognitive impairment in schizophrenia.[7] First, the timing of when deficits emerge is not well characterized. Therefore, it is unclear whether deficits evolve during specific developmental periods. The neurodevelopmental model of schizophrenia posits deviations in cognitive development many years before the emergence of overt clinical symptoms.[8,9] Central to this model is the idea of dynamic developmental processes whereby early pathologic processes interact with normal developmental events, leading to progressively abnormal function.[8,9] However, evidence of these dynamic processes has proved elusive because previous studies have not been able to comprehensively chart cognition from childhood to adulthood. Adolescence is a critical risk period for schizophrenia,[8,9] and there is evidence for abnormal brain changes during this developmental period.[10] Yet, few studies permit examination of cognitive development between late childhood and early adolescence,[6,11] and studies spanning early childhood or late adolescence are rare, with mixed results.[12,13]

Second is the question of whether individuals with subclinical psychotic experiences have normal cognitive development. Cross-sectional studies[14,15] of clinical high-risk samples have shown that individuals who transition to the clinical disorder manifest greater deficits in the domains of processing speed, memory, and working memory than those who do not. Moreover, subclinical psychotic symptoms have been associated cross-sectionally with lags in verbal and complex cognitive abilities.[16] Longitudinal studies of clinical high-risk samples have also shown that deficits in attention, working memory, and declarative memory are particularly indicative of later psychotic disorder.[17] Moreover, moderate deficits in these high-risk individuals compared with first-episode patients suggest that cognitive decline may occur before transition.[18] However, longitudinal studies are few, and most have short follow-up periods.[19,20]

A third question is how specific the cognitive deficits are to schizophrenia. Cognitive deficits have been identified in various psychiatric disorders,[21] but the extent and course of deficits appear to differ between disorders.[5,22] Major depression and bipolar disorder have generally been associated with milder deficits than schizophrenia[21] or with even above-average intellect in the case of bipolar disorder.[23] However, it remains unclear how these deficits develop and whether a course of increasing impairment is specific to schizophrenia.

Key Points

Question What is the course of cognitive functions between infancy and early adulthood in individuals with psychotic disorders, psychotic experiences, and depression?

Findings In this longitudinal birth cohort study of cognitive functioning at ages 18 months and 4, 8, 15, and 20 years that included 4322 participants, individuals with psychotic disorder—but not psychosis with depression, psychotic experiences, and depression—showed large and increasing IQ deficits as well as slowed developmental growth in specific cognitive functions, such as working memory.

Meaning The origins of psychotic disorder involve dynamic developmental processes, affecting a range of cognitive functions and leading to increasing dysfunction throughout the first 2 decades of life.

Previous longitudinal cognitive studies have been unable to answer these questions. The use of measures of scholastic achievement or IQ proxies rather than standard measures has limited the conclusions that can be drawn from such studies. Moreover, the use of different cognitive tests across ages has made it difficult to establish true cognitive change. In addition, failure to assess cognitive functioning before adolescence, when prodromal symptoms are likely to first manifest, may lead to underestimates of the magnitude of cognitive decline that precedes illness onset. Finally, few studies have measured cognitive functioning longitudinally in other psychiatric disorders.

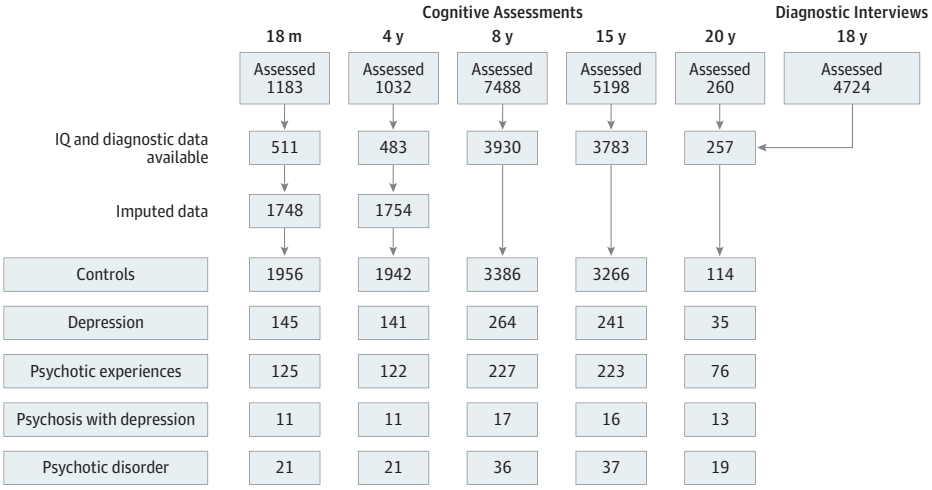
As part of an ongoing population-representative longitudinal study (the Avon Longitudinal Study of Parents and Children [ALSPAC]), we mapped IQ change from infancy (18 months) through early adulthood (20 years). We then focused on the period encompassing adolescence (age range, 8-20 years) using identical measures of IQ and specific cognitive functions across ages. Individuals with psychotic disorder, psychosis with depression, subclinical psychotic experiences, and depression were compared with controls.

Methods

Sample

The sample comprised individuals from the ALSPAC cohort. ALSPAC recruited 14 541 pregnant women residing in Avon, England, with expected dates of delivery between April 1, 1991, and December 31, 1992, resulting in 14 062 live births.[24,25] The study website (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/) contains details of all data available. Regular data collection has been ongoing since September 6, 1990. The dates of analysis were September 2015 to July 2016. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the local research ethics committees. All participants or their parents provided written informed consent.

Figure 1. Data Available at Ages 18 Months and 4, 8, 15, and 20 Years



Shown is IQ change from infancy through childhood, adolescence, and early adulthood.

IQ Change From Infancy Through Childhood, Adolescence, and Early Adulthood

We used data from all available individuals who had undergone cognitive testing during at least 1 assessment wave (18 months and 4, 8, 15, and 20 years) and had also undergone diagnostic interviewing at age 18 years. Variable numbers of individuals were available for analyses at each time (511 at age 18 months, 483 at age 4 years, 3930 at age 8 years, 3783 at age 15 years, and 257 at age 20 years). Full details are shown in **Figure 1**.

Cognitive Developmental Change Between Ages 8 and 20 Years

A total of 4724 young adults attended the assessment wave at age 18 years and underwent extensive psychological testing, including the Psychosis-Like Symptom Interview (PLIKSi).[26] Based on the PLIKSi, a case-control sample of 260 individuals (130 at high risk for psychosis, with psychotic experiences present, and 130 controls with psychotic experiences absent) underwent cognitive testing at age 20 years.[27] All those who were rated as having psychotic experiences at age 18 years and a random sample of participants who were rated as not having any psychotic experiences were invited for testing at age 20 years. Of this case-control sample of 260 individuals, 228 participants who had also undergone cognitive testing at age 8 years were available for analyses and are henceforth referred to as the high-risk longitudinal sample (eFigure 1 in the Supplement).

Measures

Psychotic Experiences

The semistructured PLIKSi draws on the Schedule for Clinical Assessment in Neuropsychiatry (SCAN). An introductory section on unusual experiences comprising 6 questions on derealization, depersonalization, self-unfamiliarity, dysmorphophobia, partial object perception, and other nonspecific perceptual abnormalities is followed by questions eliciting the following core psychotic experiences: hallucinations (visual, auditory), delusions (spied on, persecution, thoughts read, reference, control, grandiosity, or unspecified), and experiences of thought interference. Cross-questioning was used to establish the presence of symptoms, and coding followed glossary definitions and rating rules for SCAN. Interviewers were specially trained psychology graduates. Interviewers rated psychotic experiences as not present, suspected, or definite. Unclear responses after probing were always "rated down," and symptoms were rated as definite only when a clear example was provided. One of us (S.Z.) rated samples of recorded interviews every 2 months to ensure correct ratings by interviewers and to provide feedback. He also met with a group of 4 psychiatrists (G.L. and other nonauthors) at regular intervals throughout the course of the study to ensure agreement on ratings. If any interviewer's level of agreement with the criterion standard (clinician ratings) dropped below 90%, he or she received additional training.

Psychotic Disorder

If interviewers rated experiences as suspected or definitely psychotic, they also asked about frequency, help seeking, age at onset, attributions, and influence on affect, social function, and educational or occupational function (Measurement of Psychotic Experiences Using the PLIKSi in eMethods in the Supplement). Individuals were classified as having a psychotic disorder if they reported definite psychotic experiences not attributable to the effects of sleep or fever that had occurred at least once per month over the previous 6 months and either caused severe distress, had a markedly negative influence on social or occupational function, or led to help seeking. Individuals also met diagnostic criteria for psychotic disorders as defined by the *DSM-IV* and *International Classification of Disease and Related Health Problemss, Tenth Revision* because they experienced regular psychotic phenomena that caused them severe distress or substantially impaired their functioning.

For interrater reliability, the interviewers recorded audio interviews at 3 times approximately 6 months apart across the

clinic duration (75 interviews in total). The mean κ value of psychotic experiences was 0.83, with no evidence of differences across time. Test-retest reliability was assessed using 162 individuals reinterviewed after approximately 47 days (κ = 0.76, SE = 0.08), 46 of whom were reinterviewed by the same interviewer (κ = 0.86, SE = 0.14).

Depression

Depression was measured at age 18 years using the computerized version of the Clinical Interview Schedule-Revised,[28] which derives a diagnosis of depression according to *International Classification of Diseases and Related Health Problems, Tenth Revision* criteria.[29] The Clinical Interview Schedule-Revised establishes the severity of core symptoms of depressive disorders (depression, depressive thoughts, fatigue, and sleep and concentration problems) occurring in the previous month. The Clinical Interview Schedule-Revised has been widely used within community samples and is fully standardized and reliable as a self-administered computerized measure.[28,30,31]

Cognitive Functioning

Trained psychologists administered all cognitive tests. IQ was assessed at age 18 months using the Griffiths Mental Development Scales-Revised,[32] age 4 years using the Wechsler Preschool and Primary Scale of Intelligence-Revised,[33] age 8 years using the Wechsler Intelligence Scale for Children-Third Edition (WISC-III),[34] age 15 years using the Wechsler Abbreviated Scale of Intelligence,[35] and age 20 years using the WISC-III.[34] eTable 1 in the Supplement lists available tests, and eTable 2 in the Supplement summarizes tests. Full-scale, verbal, and nonverbal IQ scores were calculated. Nonverbal IQ was not available at 18 months. To examine developmental growth in specific cognitive functions, identical versions of the WISC-III digit symbol coding subtest to measure processing speed, digit span subtest to measure working memory, vocabulary subtest to measure language, and block design subtests to measure visuospatial ability, as well as the sky search task from the Test of Everyday Attention for children[36] to measure attention, were administered at ages 8 and 20 years. The WISC-III subtests were piloted on a sample of adults before the study to rule out ceiling effects.

Confounders

We examined age, sex, maternal education, and medication prescription as confounders. While all participants underwent testing during the same year at each assessment wave, they were not tested at exactly the same age. Prescription of medications for psychotic symptoms was ascertained during the PLIKSi.

Statistical Analysis

Our analyses compared the following 5 mutually exclusive groups based on clinical interviews at age 18 years: (1) psychotic disorder, (2) psychosis with depression (comorbid psychotic disorder and depression), (3) psychotic experiences, (4) depression, and (5) controls. Individuals comorbid for psychotic experiences and depression were assigned to the depression group in accord with a hierarchy based on clinical case status whereby clinical depression takes precedence over subclinical psychotic experiences.

IQ Change From Infancy Through Childhood, Adolescence, and Early Adulthood

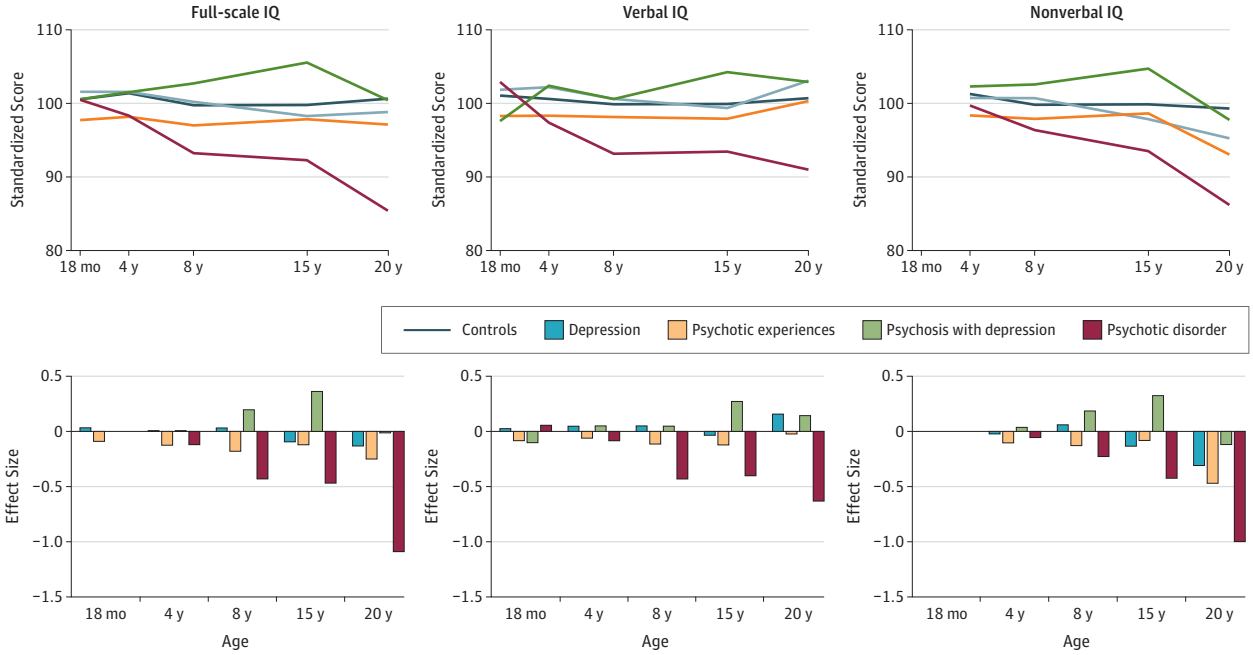
Standardized full-scale and verbal IQ scores from all available individuals at ages 18 months and 4, 8, 15, and 20 years, as well as nonverbal IQ at ages 4, 8, 15, and 20 years, were used to chart cognitive functioning throughout development (eTable 1 in the Supplement). Multilevel random regression analysis was applied in a software program (Stata, version 14; StataCorp LP) using the *mixed* command to fit linear mixed models. All models included fixed effects for group (psychotic disorder, psychosis with depression, psychotic experiences, depression, and control) and age (18 months and 4, 8, 15, and 20 years), group-by-age interactions, and random effects for age. Cohen *d* effect size[37] (ES) was computed using marginal means obtained during postestimation procedures. Following Cohen, ES of 0.2 was interpreted as reflecting small effects, 0.5 as reflecting medium effects, and 0.8 as reflecting large effects. Data were imputed for full-scale, verbal, and nonverbal IQ at ages 18 months and 4 years using multiple imputation analysis with chained equations. Twenty-eight measures were included in the imputation model, and 50 data sets were imputed (Data Imputation in eMethods in the Supplement).

Sensitivity analyses were conducted to determine whether the different sampling frame at age 20 years could lead to bias in the results. The sampling frame at 18 months and 4, 8, and 15 years was the whole ALSPAC sample (approximately 14 062 individuals). At age 20 years, the sampling frame was 4724 individuals interviewed with the PLIKSi at age 18 years. Probability weights were calculated by taking the inverse of the probability of being a case (psychotic experiences present) or control (psychotic experiences absent) at age of inclusion into the study. Then, only individuals with data available at age 20 years were included in the analyses.

Cognitive Development Between Ages 8 and 20 Years

Full-scale, verbal, and nonverbal IQ scores were used to examine change in general cognitive functions between childhood (age 8 years) and adulthood (age 20 years) in the high-risk longitudinal sample (eFigure 2 in the Supplement). Raw scores on the digit symbol coding, digit span, vocabulary, block design, and sky search task were used to examine cognitive development in specific functions. Raw scores rather than age-corrected scaled scores were used. Scaled scores are the same at all ages to facilitate interindividual comparisons, thus obscuring growth over time.[6] In contrast, the use of raw scores enables measurement of cognitive development. Multilevel random regression analysis was applied as above (see IQ Change From Infancy Through Childhood, Adolescence, and Early Adulthood under Statistical Analysis). Models were adjusted for potential confounders (see Confounders under Measures) and subsequently for all other cognitive tests. Because multiple cognitive tests were used, a Bonferroni-corrected significance level of 2-sided $P < .008$ (0.05 divided by 6) (ie, the

Figure 2. Standardized Scores and Effect Size by Group at Ages 18 Months and 4, 8, 15, and 20 Years



Results using imputed scores at ages 18 months and 4 years are presented owing to an Avon Longitudinal Study of Parents and Children policy for presenting data with small cell counts. Analyses of raw nonimputed data generated similar results.

number of cognitive domains measured [IQ, processing speed, working memory, language, visuospatial ability, and attention]) was adopted to allow for repeated testing, although this significance is likely to be conservative given that the tests are correlated. The Cohen *d* ES was computed as above (see IQ Change From Infancy Through Childhood, Adolescence, and Early Adulthood under Statistical Analysis).

Results

In total, 4322 participants were available for analyses in this longitudinal birth cohort study. These included 511 (238 male [46.6%]) at age 18 months (mean [SD] age, 1.53 [0.03] years), 483 (229 male [47.4%]) at age 4 years (mean [SD] age, 4.07 [0.03] years), 3930 (1679 male [42.7%]) at age 8 years (mean [SD] age, 8.65 [0.29] years), 3783 (1686 male [44.6%]) at age 15 years (mean [SD] age, 15.45 [0.27] years), and 257 (90 male [35.0%]) at age 20 years (mean [SD] age, 20.06 [0.55] years).

IQ Change Through Infancy, Childhood, Adolescence, and Early Adulthood

Figure 2 shows standardized full-scale, verbal, and nonverbal IQ scores and ES at 18 months and 4, 8, 15, and 20 years, with associated model statistics listed in the **Table**. The psychotic disorder group showed increasing full-scale, verbal, and nonverbal IQ deficits from 18 months to 20 years, with overall declines in full-scale IQ equal to −1.09 SD (P = .02), verbal IQ equal to −0.69 SD (P = .07), and nonverbal IQ equal to −0.94 SD (P = .008).

The depression group showed an increasing nonverbal IQ deficit from 18 months to 20 years, with an overall decline equal to −0.29 SD (P = .04). There was weak evidence for cognitive deficits in the psychotic experiences group and the psychosis with depression group.

Sensitivity analyses generated similar results (eFigure 2 and eFigure 3 in the Supplement). Repeating the analyses using only individuals with data available at all times also generated similar results (eFigure 4 in the Supplement).

Cognitive Development Between Ages 8 and 20 Years

Full-scale, Verbal, and Nonverbal IQ

Figure 3 shows full-scale, verbal, and nonverbal IQ scores and ES at ages 8 and 20 years, with model statistics in eTable 3A in the Supplement. The psychotic disorder group showed significant main effects on full-scale IQ (ES = −1.17, P = .004) and verbal IQ (ES = −0.99, P = .007), as well as significant group-by-age interactions on full-scale IQ (effect size of change [ESΔ] = −0.54, P = .005) and nonverbal IQ (ESΔ = −0.61, P = .002), suggesting increasing full-scale and nonverbal IQ deficits and a static verbal IQ deficit. The psychotic experiences group showed main effects on full-scale IQ (ES = −0.45, P = .01) and verbal IQ (ES = −0.31, P = .01), as well as a group-by-age interaction on nonverbal IQ (ESΔ = −0.22, P = .04), which did not reach Bonferroni-corrected significance. No statistically significant results were seen in the psychosis with depression group and the depression group.

Individual reliable change indexes[38] were calculated for full-scale IQ between ages 8 and 20 years. Most individuals with psychotic disorder (13 of 16 [81.3%]) showed a decline in IQ,

Table. Group and Group-by-Age Interaction Effects of Multilevel Random Regression Analysis on Full-scale, Verbal, and Nonverbal IQ at Ages 18 Months and 4, 8, 15, and 20 Years

Variable	Psychotic Disorder					Psychosis With Depression					Psychotic Experiences					Depression				
	Mean Score	Mean Score Δ	β (SE)	*P* Value	Effect Size	Effect Size Δ	Mean Score	Mean Score Δ	β (SE)	*P* Value	Effect Size	Effect Size Δ	Mean Score	Mean Score Δ	β (SE)	*P* Value	Effect Size	Effect Size Δ	Mean Score	Mean Score Δ	β (SE)	*P* Value	Effect Size	Effect Size Δ
Group effect																								
Full-scale IQ	94.9	NA	−0.06 (4.78)	.99	−0.23	NA	103.0	NA	0.01 (5.95)	.99	0.12	NA	98.0	NA	−2.82 (2.01)	.16	−0.11	NA	100.0	NA	1.04 (1.76)	.56	−0.01	NA
Verbal IQ	95.7	NA	1.85 (4.14)	.66	−0.18	NA	101.5	NA	−3.43 (6.28)	.59	0.05	NA	98.2	NA	−2.75 (1.91)	.15	−0.08	NA	100.8	NA	0.79 (1.62)	.63	0.02	NA
Nonverbal IQ	95.7	NA	−1.57 (4.23)	.71	−0.22	NA	103.2	NA	1.01 (5.68)	.86	0.15	NA	98.2	NA	−2.93 (1.92)	.12	−0.10	NA	99.5	NA	−0.56 (1.67)	.74	−0.03	NA
Group-by-age interaction																								
Full-scale IQ	NA	−15.1[a]	−0.58 (0.25)[a]	.02[a]	NA	−1.09[a]	NA	−0.1	0.16 (0.28)	.57	NA	−0.01	NA	−0.6	0.06 (0.11)	.55	NA	−0.16	NA	−2.8	−0.16 (0.11)	.13	NA	−0.17
Verbal IQ	NA	−11.9	−0.42 (0.23)	.07	NA	−0.69	NA	5.3	0.33 (0.31)	.29	NA	0.25	NA	2.0	0.10 (0.11)	.34	NA	0.06	NA	1.2	−0.07 (0.10)	.49	NA	0.13
Nonverbal IQ	NA	−13.5[a]	−0.64 (0.24)[a]	.008[a]	NA	−0.94[a]	NA	−4.5	−0.09 (0.31)	.78	NA	−0.15	NA	−5.3	−0.07 (0.12)	.54	NA	−0.37	NA	−5.5[a]	−0.24 (0.12)[b]	.04[a]	NA	−0.29[a]

Abbreviation: NA, not applicable.

[a] $P < .05$.

and this decline exceeded the established threshold for reliable change[38] in 10 of 16 (62.5%) individuals with psychotic disorder.

Specific Cognitive Functions

Figure 3 shows raw processing speed, working memory, language, visuospatial ability, and attention scores, as well as ES at ages 8 and 20 years, with model statistics listed in eTable 3A in the Supplement. The psychotic disorder group showed statistically significant main effects on language (ES = −0.87, $P = .005$) and visuospatial ability (ES = −0.90, $P = .001$), suggesting static deficits in these domains. The psychotic experiences group also showed main effects on language (ES = −0.33, $P = .02$) and visuospatial ability (ES = −0.44, $P = .01$), which did not reach Bonferroni-corrected significance. Statistically significant group-by-age interactions for the psychotic disorder group on processing speed (ESΔ = −0.68, $P = .001$), working memory (ESΔ = −0.59, $P = .004$), and attention (ESΔ = −0.44, $P = .001$) tests suggested increasing lags in these domains. The psychotic experiences group showed significant group-by-age interactions on processing speed (ΔES = −0.29, $P = .02$) and attention (ΔES = −0.16, $P = .04$), which did not reach Bonferroni-corrected significance. No statistically significant results were seen in the psychosis with depression group or the depression group.

We further examined the working memory and attention tasks by examining their subcomponents (eFigure 5 and eResults in the Supplement). The psychotic disorder group showed statistically significant lags on both the maintenance and manipulation working memory subtasks as well as in the selective attention subtask, while the deficit in sustained attention showed no change.

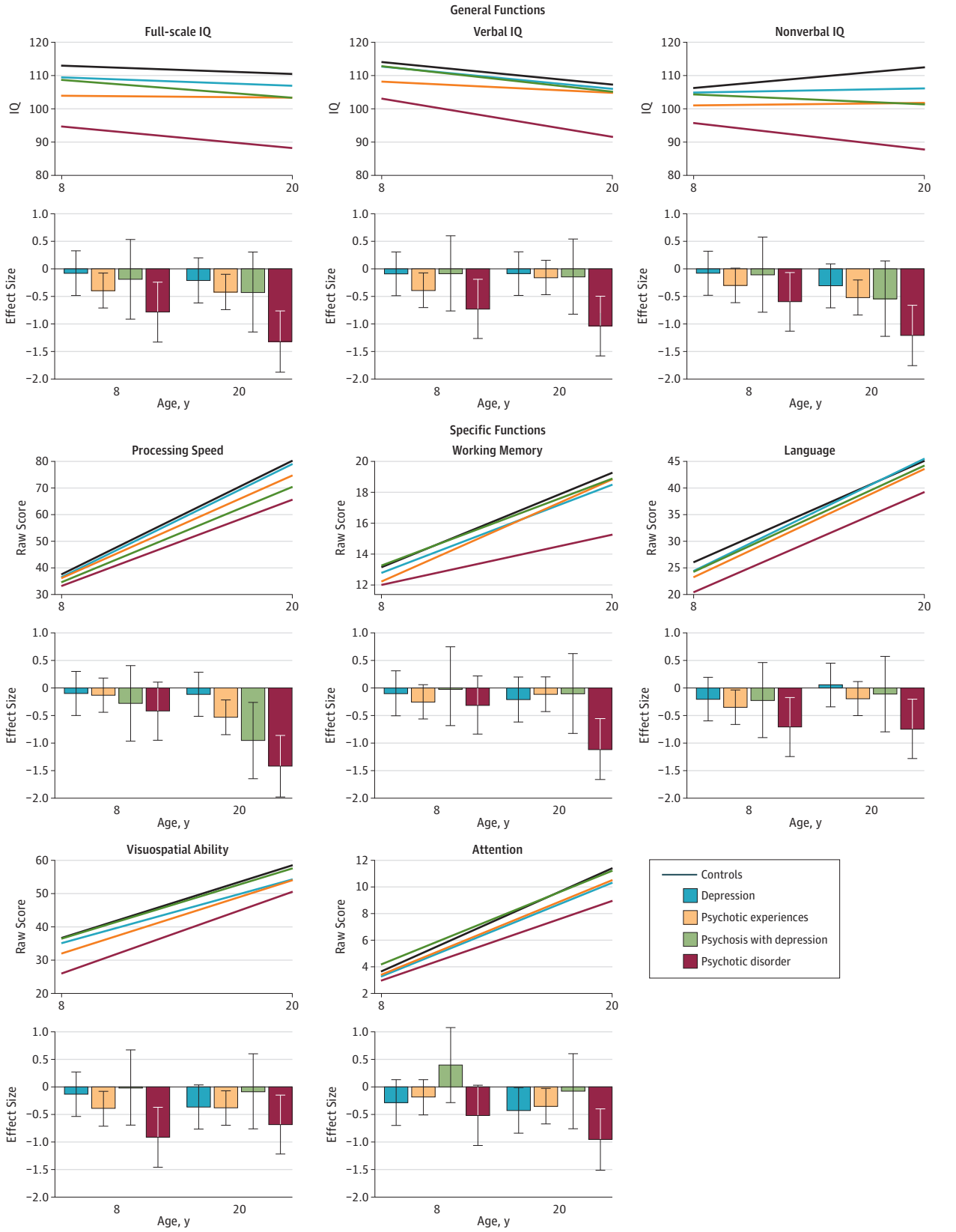
Adjusting for Confounders

After adjusting for age, sex, maternal education, and medication prescription (4 participants reported during the PLIKSi being prescribed medication at age 18 years) (eTable 3B in the Supplement), main effects for the psychotic disorder group on full-scale IQ (ES = −0.96, $P = .04$), verbal IQ (ES = −0.83, $P = .03$), language (ES = −0.59, $P = .09$), and visuospatial ability (ES = −0.53, $P = .04$), as well as the group-by-age interaction on full-scale IQ (ESΔ = −0.54, $P = .01$), were no longer statistically significant at the Bonferroni-corrected level, but the ES remained medium to large. Group-by-age interactions for the psychotic disorder group on nonverbal IQ (ESΔ = −0.64, $P = .002$), processing speed (ESΔ = −0.73, $P = .001$), working memory (ESΔ = −0.65, $P = .006$), and attention (ESΔ = −0.57, $P < .001$) remained significant. The ES for the psychosis with depression group and the psychotic experiences groups remained small.

Adjusting for Other Cognitive Tests

Main effects for the psychotic disorder group on language (ESΔ = −0.71, $P = .04$) and visuospatial ability (ESΔ = −0.37, $P = .15$) were no longer statistically significant at the Bonferroni-corrected level when adjusting for other cognitive tests (eTable 3C in the Supplement). Group-by-age interactions on processing speed (ESΔ = −0.82, $P = .001$), working memory (ESΔ = −0.70, $P = .005$), and attention (ESΔ = −0.50, $P < .001$) remained significant.

Figure 3. Scores and Effect Size for General and Specific Cognitive Functions by Group at Ages 8 and 20 Years



Error bars represent 95% CIs.

Discussion

By using a population-based cohort followed prospectively from birth, this study provides the strongest evidence to date of cognitive decline in individuals with psychotic disorder. Our findings advance knowledge in several ways.

First, we traced the course of IQ through infancy, childhood, adolescence, and early adulthood in individuals with psychotic disorder, psychosis with depression, psychotic experiences, and depression. Only individuals with psychotic disorder showed progressive IQ deficits. Verbal IQ declined in early childhood and remained stable thereafter, whereas decline in full-scale IQ and nonverbal IQ continued through adolescence and early adulthood. Our findings suggest that psychotic disorder is associated with decline in not only nonverbal but also verbal cognitive functions, albeit during different developmental periods. These findings extend those of the British 1946 birth cohort[39] by showing static verbal deficits and increasing nonverbal deficits beyond adolescence. Cognitive impairment in schizophrenia has been hypothesized to be the product of 2 processes (static deficit and increasing lag[6]), but previous studies were limited by the developmental periods during which data were available. Our findings, spanning the first 2 decades of life, suggest that cognitive deficits associated with psychotic disorder may be due to a single, dynamic process. Increasing lags may be present across cognitive functions, with the largest lags seen during potentially different critical developmental periods.

Second, we focused on the period encompassing adolescence (age range, 8-20 years) using identical cognitive measures across ages. Developmental growth was ubiquitous across groups and cognitive functions, but the rate of growth differed. Individuals with psychotic disorder showed reduced growth on measures of processing speed, working memory, and attention. To our knowledge, this is the first time identical cognitive tests have been administered over this developmental period, one hypothesized to be of critical risk for schizophrenia.[8] Our findings suggest that increasing cognitive impairment during this developmental period is not due to an absolute deterioration in function over time. Rather, individuals do not keep up with developmentally normal growth. Our findings of dynamic developmental processes, leading to progressively abnormal cognitive function, are in line with a neurodevelopmental model.[8] These findings also extend those of the Dunedin birth cohort[6] by showing that an absolute deterioration in cognitive functions remains unlikely even in adolescence.

Third, we compared individuals having psychotic disorder, psychosis with depression, psychotic experiences, and depression with controls. Previous findings regarding the specificity of increasing cognitive impairment are mixed, with reports of IQ decline in affective psychoses,[13] processing speed delays in psychotic experiences,[40] and small, general deficits in depression.[5,6] In our sample, individuals with psychosis with depression, psychotic experiences, and depression showed small cognitive lags and deficits in certain functions. Only individuals with psychotic disorder demonstrated large, widespread, progressive deficits. The psychosis with depression group outperformed those with psychotic disorder across all functions but also showed only small deficits compared with controls except in processing speed.

Similar findings have been reported previously,[41,42] although there have been reports of large declines in verbal ability in individuals with affective psychoses.[13] One possible reason for these discrepant findings may be differences in sample ascertainment. While the sample in the study by MacCabe et al[13] comprised male conscripts who had been admitted to a hospital, our sample comprised both sexes from a general population cohort. Moreover, while we were able to establish the simultaneous occurrence of psychotic disorder and depression at age 18 years, we were not able to distinguish between individuals in whom these symptoms began simultaneously and those in whom depression preceded psychosis or vice versa. Future studies that use dimensional approaches of psychopathology and are able to disentangle the timing of depressive and psychotic symptoms are needed to better elucidate the cognitive correlates of psychosis with and without affective symptoms. Altogether, these findings suggest that psychotic disorders with and without accompanying affective symptoms have different causes.[43] While affective and nonaffective psychoses may share certain susceptibility genes,[44] additional genetic or environmental factors may lead to distinct neurodevelopmental profiles.[43]

Our findings have important theoretical and clinical implications. The extent and timing of cognitive deficits in psychotic disorder vary between functions. Verbal functions may decline during early childhood and remain stable thereafter, while deficits in nonverbal functions may continue to increase through adolescence and early adulthood. Early neurodevelopmental insults may lead to verbal deficits that emerge early and interact with later neurodevelopmental processes, leading to increasing deficits in functions that mature later. Alternatively, early verbal deficits may impede normal developmental growth in other functions, leading to increasing lags during adolescence and beyond. Clinically, our findings highlight the importance of early intervention for cognitive deficits. Verbal abilities may be more amenable to change during childhood, while interventions during adolescence may be most effective for nonverbal abilities.

Limitations

This study has some limitations. First, the analyses spanning infancy and adulthood used variable numbers of individuals available at different ages, as well as at certain ages only small groups with psychotic disorder. Therefore, while our sample was drawn from a well-characterized, population-based birth cohort, the results require replication in independent samples. Future studies using racially/ethnically diverse samples are also needed because 95% of the ALSPAC sample comprises Britons of white race/ethnicity. However, our imputations suggested that missing data at younger ages were unlikely to have led to bias in the results. Moreover, the findings of the longitudinal high-risk sample at ages 8 and 20 years corroborate those from infancy to adulthood (eFigure 6 in the Supplement). Second, while we classified those comorbid for psychotic experiences and de-

pression into the depression group, this group may have a cognitive profile distinct from those with depression without psychotic experiences. However, supplementary analyses separating out this group suggest that they do not differ substantially or consistently across domains from those with psychotic experiences or depression alone (eFigures 7, 8, 9, and 10 in the Supplement). Third, depression was ascertained using a self-administered questionnaire, and our results require replication using a clinical interview. Future follow-up studies will also be able to disentangle the timing of affective and psychosis symptoms because psychotic disorder may later develop in some individuals in the depression group. Fourth, a recent study[45] reported that schizophrenia polygenic risk score is associated with nonparticipation in the ALSPAC. However, the effect was small, with individuals being 11% to 15% less likely to attend follow-up visits.[45] Because schizophrenia polygenic risk score has also been associated with poorer cognition[46] and greater cognitive decline,[47] our results may only underestimate, rather than overestimate, the cognitive deficit or decline associated with psychotic disorder. Moreover, the ES data reported herein closely approximate those of multiple meta-analyses of cognitive functioning in schizophrenia,[1,3,4,48] and our imputations and sensitivity analyses suggest that missing data are unlikely to have led to bias.

Conclusions

Individuals with psychotic disorder showed a dynamic course of cognitive impairment throughout the first 2 decades of life. Verbal functions declined during infancy, whereas nonverbal abilities showed reduced growth during adolescence. Future efforts to elucidate the pathophysiological processes underlying this progressive dysfunction and the developmental periods during which it occurs will inform early detection and intervention strategies.

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